*Immunology* 2004 **113** 23–25 doi:10.1111/j.1365-2567.2004.01963.x

**COMMENT**

# CD137: costimulator turns suppressor?

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**Keywords** CD137; costimulator; immunotherapy; suppressor

The complete activation and differentiation of T cells into effector and memory cells is rarely achieved through signalling by the T cell receptor (TCR) alone.[1,2] This is due probably to the relative paucity of TCR ligands and low affinity of interaction between the TCR and its peptide-major histocompatibility complex (MHC) ligands.[3] The interaction of additional receptors, known as costimulatory receptors, on T cells with their cognate ligands on antigen-presenting cells (APCs) is required for T cells to become fully activated.[4,5] The engagement of costimulatory molecules amplifies the signals triggered by the TCR, resulting in enhanced proliferation, cytokine production and survival of activated T cells. Furthermore, costimulatory signals are necessary to prevent the induction of anergy, a state of unresponsiveness that precludes appropriate activation of T cells upon secondary encounter with antigen.[6] In this issue of *Immunology*, Foell and colleagues, surprisingly, show that triggering of the costimulatory receptor, CD137 (4–1BB) inhibits immune responses and this property can be utilized to ameliorate autoimmune conditions.[7]

Co-stimulatory receptors can be classified into two groups.[4,5] The first group, exemplified by CD28 and ICOS, are members of the Ig superfamily which bind to distinct members of the B7 family of cell surface proteins. The second class of costimulatory receptors belongs to the tumour necrosis factor (TNF) receptor (TNFR) superfamily and includes molecules such as CD27, CD30, CD40, CD134 (OX40) and CD137 (4–1BB). This group of TNFR superfamily members lacks the death domain present in other members of this superfamily, such as the p55 TNFR and CD95 (Fas). Under certain circumstances engagement of death domain-lacking TNFR superfamily members can result in the induction of cell death by a mechanism that is not fully understood.[8] The ligands of TNFR superfamily members are trimeric membrane proteins belonging to the TNF superfamily, some of which are also produced as soluble proteins.[9]

Different costimulatory receptor–ligand interactions appear to be required at distinct stages of the immune response. For example, CD28 and CD27, which are expressed on naive T cells, are necessary for the initial proliferation and survival of T cells.[10–12] In contrast to CD28 and CD27, ICOS, CD134 and CD137 are expressed on activated T cells and engagement of these receptors by their cognate ligands influences effector functions and T cell numbers during the late stage of the primary response.[10,13,14] Furthermore, secondary, or recall responses are less dependent on CD28 costimulation but remain reliant on other costimulatory receptors, such as CD134, CD137 and ICOS.[15–17]

There is evidence that $CD4^+$ and $CD8^+$ T cell responses are influenced to varying degrees by different costimulatory receptors. $CD8^+$ but not $CD4^+$ T cell responses generated against lymphocytic choriomeningitis virus (LCMV), or influenza virus are diminished in CD137 ligand (CD137L)-deficient mice.[10,18] Conversely, $CD4^+$ T responses generated against LCMV and influenza virus are compromised in CD134-deficient mice, but $CD8^+$ T cell responses appear to remain intact.[19] This is consistent with data demonstrating preferential costimulation of $CD4^+$ and $CD8^+$ T cells by agonistic CD134 and CD137 monoclonal antibodies (mAbs), respectively.[20,21] The demonstration that CD137 is a potent costimulator of $CD8^+$ T cells has led to the utilization of agonistic CD137-specific mAbs for the augmentation of weak $CD8^+$ T cell responses, such as those elicited by tumour-associated antigens. Several studies have shown that the administration of agonistic CD137 mAbs trigger the rejection of weakly immunogenic murine tumours.[21–23] In an approach that is more relevant to human cancers, Wilcox *et al.*[23] showed that administration of agonistic CD137 mAb and tumour-derived $CD8^+$ T cell peptide epitopes promoted the regression of established, poorly immunogenic tumours in mice. Interestingly, CD137 stimulation *in vivo* appears to broaden the $CD8^+$ T cell response by preferentially enhancing the expansion of $CD8^+$ T cells that recognize subdominant epitopes.[24] It remains to

Received 9 July 2004; revised 13 July 2004; accepted 13 July 2004

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be determined whether agonistic CD137 mAbs promote $CD8^+$ T cell responses *in vivo* entirely by direct activation of $CD8^+$ T cells, or additionally by stimulation of natural killer (NK) and dendritic cells, which also express CD137.[25–27]

In contrast with the ability of agonistic CD137 mAbs to augment weak immune responses mediated by $CD8^+$ T cells, several recent studies, including one by Foell and colleagues[7] in this issue of *Immunology*, demonstrate that these same mAbs are effective in ameliorating certain experimental autoimmune diseases. Adminstration of agonistic CD137 mAbs to mice blocked lupus-like autoimmune disease,[28,29] reduced the incidence and severity of experimental autoimmune encephalomyelitis[30] and, in this issue, inhibited collagen-induced arthritis[7] (this issue). How, then, can a costimulatory receptor function as a suppressor?

Autoreactive $CD4^+$ T cells play a central role in the initiation and progression of autoimmune diseases through provision of help to self-reactive B cells for the production of autoantibodies and by activation of macrophages. An earlier study demonstrated that the administration of agonistic CD137 mAb inhibits T cell-dependent humoral responses to foreign antigens, an effect attributed to a defect in the $CD4^+$ T cell compartment.[31] Indeed, administration of CD137 mAb inhibited the production of autoantibodies in murine models of lupus and in collagen-induced arthritis, thus providing an explanation for the ability of the mAb to ameliorate the disease. Furthermore, agonistic CD137 mAbs are still capable of exerting these immune suppressive effects in CD137L-deficeint mice, thus excluding the possibility that their effects are due to inhibition of the CD137–CD137L interaction.[29] One way by which agonistic CD137 mAbs inhibit $CD4^+$ T cell responses is through promoting their deletion via activation-induced cell death. Sun *et al.*[30] demonstrated that while stimulation by agonistic CD137 mAb *in vivo* enhanced the initial proliferation of $CD4^+$ T cells, it subsequently accelerated their death. An alternative mechanism that could account for the suppressive effects of CD137 mAbs on $CD4^+$ T cells is if stimulation via CD137 expressed on $CD4^+$ T cells, dendritic cells or NK cells results in the induction of anergy in $CD4^+$ T cells.[29] In addition, agonistic CD137 mAbs may promote the generation of regulatory or suppressor cells that inhibit $CD4^+$ effector T cells, although the inability so far to adoptively transfer the suppressive effects argues against this possibility.[31] It is noteworthy that in CD137L-deficient mice $CD4^+$ T cell responses are not accentuated, as would be predicted from the effects of agonistic CD137 mAbs; in fact, they are slightly compromised.[32] The difference may reside in the disparate timing and duration of the signals triggered by the agonistic mAb when compared with the natural ligand. CD137L is expressed on activated APCs and the duration of its expression *in vivo* is likely to be highly regulated.[27] Clearly, understanding the entire repertoire of effects triggered by agonistic CD137 mAbs is imperative for their successful application in immunotherapy. This will be achieved through mechanistic studies that define in full the function of CD137.

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